A pilot study: ^{131}I-Antitenascin monoclonal antibody 81c6 to deliver a 44-Gy resection cavity boost

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The purpose of this study was to determine the feasibility and assess the efficacy and toxicity, among newly diagnosed malignant glioma patients, of administering ^{131}I-labeled murine antitenascin monoclonal antibody 81C6 (^{131}I-81C6) into a surgically created resection cavity (SCRC) to achieve a patient-specific, 44-Gy boost to the 2-cm SCRC margin. A radioactivity dose of ^{131}I-81C6 calculated to achieve a 44-Gy boost to the SCRC was administered, followed by conventional external beam radiotherapy (XRT) and chemotherapy. Twenty-one patients were enrolled in the study: 16 with glioblastoma multiforme (GBM) and 5 with anaplastic astrocytoma. Twenty patients received the targeted 44-Gy boost (±10%) to the SCRC. Attributable toxicity was mild and limited to reversible grade 3 neutropenia or thrombocytopenia (n = 3; 14%), CNS wound infections (n = 3; 14%), and headache (n = 2; 10%). With a median follow-up of 151 weeks, median overall survival times for all patients and those with GBM are 96.6 and 90.6 weeks, respectively; 87% of GBM patients are alive at 1 year. It is feasible to consistently achieve a 44-Gy boost dose to the SCRC margin with patient-specific dosing of ^{131}I-81C6. Our study regimen (^{131}I-81C6 + XRT + temozolomide) was well tolerated and had encouraging survival. To determine if selection of good-prognosis patients affects outcome associated with this approach, the U.S. Food and Drug Administration has approved a trial randomizing newly diagnosed GBM patients to either our study regimen or standard XRT plus temozolomide. *Neuro-Oncology 10, 182–189, 2008 (Posted to Neuro-Oncology [serial online], Doc. D06-00199, February 20, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-053)*

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Adults with primary malignant glioma have an unacceptably poor outcome. Although temozolomide plus radiotherapy improves survival of newly diagnosed glioblastoma multiforme (GBM) patients,[1] most patients develop tumor progression within 1–2 years. Outcome following recurrence is poor.[2] Most tumors recur at or adjacent to the site of origin, indicating that failure to eradicate local tumor growth is a major factor contributing to poor outcome.[3] For this reason, we have focused on augmenting local control to improve overall outcome by administering tumor-associated radiolabeled monoclonal antibodies (mAbs) directly into spontaneous tumor cysts, surgically

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created resection cavities (SCRCs), the intrathecal space, and solid tumors.[4–8]

Tenascin, an extracellular matrix hexabrachion glycoprotein, is expressed ubiquitously in several cancers, including high-grade gliomas, but not in normal brain.[9,10] mAb 81C6, a murine isotype 2b immunoglobulin G (IgG2b) that binds to an alternatively spliced region of tenascin,[9–12] reacts specifically with tenascin-expressing tumors.[13] When labeled with ^{131}I, 81C6 delays tumor growth and prolongs survival in flank and intracranial human xenograft models.[14,15]

An initial human experience demonstrated the specificity of ^{131}I-labeled murine 81C6 (^{131}I-81C6) mAb compared to ^{125}I-labeled nonspecific IgG2b mAb but also revealed limited intratumor penetration following intravenous or intraarterial administration.[16] Hence, subsequent studies incorporated administration into an SCRC, tumor cyst, or intrathecal space. Prior phase I studies established the maximum tolerated dose (MTD) of ^{131}I-81C6 injected into the SCRC of patients with newly diagnosed and recurrent malignant brain tumors to be 120 mCi and 100 mCi, respectively.[7,8] Phase II studies demonstrated that patients treated with ^{131}I-81C6 had favorable overall survival compared to established historical controls.[4,5]

Based on constraints of our U.S. Food and Drug Administration (FDA)-approved phase I and II studies, patients received a "fixed" dose of ^{131}I-81C6 in which the administered level of radioactivity was the same among groups of patients. As a result of this design, ^{131}I dosages were not adjusted to compensate for patient-specific variables such as SCRC volume and SCRC residence time. Dosimetry of patients treated on these studies revealed a wide range of radiation absorbed doses at the SCRC margin. Moreover, outcome correlated with delivered radiation dose to the SCRC. Specifically, patients who received less than 44 Gy were more likely to develop recurrent tumor, whereas those who received significantly more than 44 Gy were more likely to develop radionecrosis. Therefore, a 44-Gy boost to the SCRC margin was considered optimal.[17] We now report a pilot study using a novel, patient-specific dosing strategy of ^{131}I-81C6 designed to achieve a 44-Gy boost to the 2-cm SCRC margin in adults with newly diagnosed malignant gliomas.

Materials and Methods

Antibody Production and Labeling

81C6, grown in athymic mouse ascites, was purified over a Sepharose-staphylococcal protein-A column followed by polyethylenimine ion exchange chromatography. FDA manufacturing and testing guidelines for mAb products were followed for each clinical batch.[18] 81C6 was radiolabeled using a modified Iodo-Gen procedure (Pierce Chemical Company, Rockford, IL, USA). To maintain optimal immunoreactivity, 10 mg of 81C6 was used with <100 mCi doses, and 20 mg was used with ⩾100 mCi doses. All preparations had ⩾80% immunoreactivity, with ⩾95% of the label eluting as IgG on high-pressure liquid chromatography and precipitating with trichloroacetic acid.

Eligibility

Eligible patients had a confirmed histologic diagnosis of newly diagnosed supratentorial primary malignant glioma and were candidates for surgical resection. Patients with tumors that were infratentorial, diffusely infiltrating, or multifocal or that had intraventricular access or subependymal spread were ineligible. Histopathologic samples from initial surgery were centrally reviewed at Duke University Medical Center (DUMC) and tested for tenascin immunoreactivity.[5] Additional eligibility criteria included age >18 years and KPS score ⩾60%. Pregnant or lactating patients and those with iodine allergy were ineligible.

The DUMC Investigational Review Board approved this study, and each subject provided informed consent.

Patient-Specific ^{131}I-81C6 Treatment

Patients underwent a gross total resection (GTR) and placement of a Rickham reservoir and catheter into the SCRC. Contrast-enhanced MRI was obtained within 48 h of resection to confirm that residual tumor did not extend more than 1.0 cm beyond the SCRC margin. Rickham catheter patency and SCRC integrity were confirmed by injecting ^{99m}Tc-labeled albumin or diethylenetriaminepentaacetic acid into the Rickham reservoir and obtaining gamma camera images immediately and 4 and 24 h later. All preparations had immunoreactivity of more than 75%, with more than 95% of the label eluting as IgG on high-pressure liquid chromatography and precipitating with trichloroacetic acid. Patients with subgaleal or subarachnoid leakage were excluded. A 1–3 mCi dose of ^{123}I-81C6 was administered into the resection cavity 3–7 days postoperatively. Additional gamma camera images were obtained immediately, 2, 24, and 48 h later to calculate the effective half-life and biologic clearance half-life of murine 81C6. By correcting for the physical half-life of ^{131}I, ^{131}I-81C6 residence time was calculated. Postoperative MRI images 2 mm thick were used to generate a three-dimensional reconstruction of the head and SCRC (VoxelView 2.5.4; Vital Images, St. Paul, MN, USA). The calculated SCRC volume was used to estimate the initial SCRC activity, where a uniform activity concentration was assumed. Using the measured ^{131}I-81C6 residence time and SCRC volume, the radioactivity dose of ^{131}I-81C6 predicted to achieve a 44-Gy boost to the SCRC margin was calculated.

Eligible patients received four drops of saturated potassium iodine solution and 75 μg of liothyronine sodium (Cytomel; SmithKline Beecham, Pittsburgh, PA, USA) daily from 2 days before to 16 days after ^{131}I-81C6 administration. In order to administer ^{131}I-81C6, the Rickham reservoir was accessed with a 25-gauge needle using sterile technique, and up to 6 ml of SCRC cyst fluid was removed. ^{131}I-81C6 mAb was injected into the reservoir in a volume of ⩽6 ml. The reservoir and

catheter were then flushed with the previously aspirated, sterile SCRC fluid. Patients remained in radiation isolation until the whole-body ^{131}I retention was ≤30 mCi as measured by a cross-calibrated radiation survey meter.

Pharmacokinetics and Dosimetry

Prior to discharge, a brain MRI was performed and serial radionuclide gamma images as well as blood samples were obtained to assess ^{131}I biodistribution. Absorbed dose calculations for the SCRC, whole body, and bone marrow were performed using a serial, two-compartment system to model ^{131}I-81C6 pharmacokinetics, where the SCRC and whole body (exclusive of the SCRC) were assumed to be first and second compartments, respectively. Depth-dose calculations of the SCRC interface, 2-cm-thick margin, and normal brain were performed.[19]

Post-^{131}I-81C6 Radiotherapy and Chemotherapy

Approximately 1 month after ^{131}I-81C6, patients began conventional external beam radiotherapy (XRT), administered to deliver 55–60 Gy to the tumor bed over 6 weeks, followed by standard dosing schedules of chemotherapeutics, including temozolomide, lomustine, irinotecan, and etoposide, for 10–12 months. These agents were administered in a serial manner, with rotation between agents performed every 8–12 weeks.

Toxicity and Response Determinations

Patients were followed indefinitely for toxicity (Common Toxicity Criteria, version 2.0, National Cancer Institute, Bethesda, MD, USA) and survival. Initial follow-up occurred 1 month after treatment. Complete blood counts were monitored weekly for 8 weeks. Patients were reevaluated prior to initiating XRT and chemotherapy and then every 4–8 weeks during chemotherapy. Thereafter, evaluations continued every 3 months for 1 year, every 4 months for the second year, and then biannually. At each evaluation, a complete physical examination, including a detailed neurologic examination, KPS rating, complete blood count, biochemical profile, and contrast MRI, was performed. [^{18}F]Fluorodeoxyglucose (^{18}FDG) PET scans were obtained as needed. Thyroid function was assessed within 1–2 months of ^{131}I-81C6 and every 6–12 months thereafter. Human antimouse antibody (HAMA) titers were measured within 6 months of ^{131}I-81C6 administration.

Quality of life (QoL) was assessed using the Functional Assessment of Cancer Therapy–Brain Cancer subscale (FACT-BR)[20] prior to study treatment, within 3 months of ^{131}I-81C6 administration, and then every 3 months thereafter. Patients also underwent a neurocognitive test battery that included the Ruff 2 & 7 Test,[21] Hopkins Verbal Learning Test-Revised,[22] and Trail Making Test A and B.[23] Neurocognitive assessments were conducted by doctorate-level neuropsychologists with extensive neuro-oncology experience and were performed prior to study treatment, within 3 months of ^{131}I-81C6 administration, and then every 6–12 months thereafter. Patients were encouraged, although not required, to complete QoL and neurocognitive assessments.

Acute and delayed neurotoxicity was assessed primarily based on detailed neurologic evaluations performed at each evaluation as described above, integrated with QoL, neurocognitive, and radiologic assessments. Although seizures were recorded, they were not classified as neurotoxicity because of their expected frequency in this disease setting. The precise etiology of neurotoxicity following ^{131}I-81C6 was difficult to define because neither clinical nor radiographic features reliably distinguished recurrent tumor from treatment-induced necrosis. Although stereotactic biopsy is limited by volume sampling, it remains the definitive diagnostic tool of focal brain lesions. Therefore, the etiology of observed neurotoxicity was based on stereotactic biopsy whenever possible.

Progressive disease was defined by (1) >25% increase of enhancing tumor cross-sectional area or radiographically new lesions that were also hypermetabolic on ^{18}FDG PET scan; (2) clinical deterioration and a >25% increase in enhancing tumor or radiographically new lesions; or (3) biopsy-proven recurrent tumor.

Statistical Analysis

The primary objective of this pilot study was to determine the feasibility of administering ^{131}I-81C6 to achieve a 44-Gy boost to the SCRC margin in newly diagnosed malignant glioma patients. Overall survival and 1-year overall survival were additional outcome measures. The method of Kaplan and Meier[24] was used to estimate survival distributions, where survival was measured from the date of ^{131}I-81C6 administration to death or last contact.

Results

Patient Characteristics

The study population included 21 newly diagnosed malignant glioma patients treated at DUMC between March 2002 and February 2004 (Table 1). Approximately 5% of screened patients were excluded due to subgaleal leakage on the postoperative flow study, primarily due to SCRC proximity to the ventricular system.

^{131}I-81C6 was administered prior to XRT in 17 patients and after XRT in three patients. Twenty patients received systemic chemotherapy after ^{131}I-81C6 (Table 1). One patient opted not to receive either XRT or systemic chemotherapy. With a median follow-up of 151 weeks, seven patients (33%) remained alive: five with anaplastic astrocytoma (AA) and two with GBM. Among these surviving patients, two were alive with progressive tumor, and five remained tumor free.

Table 1. Patient characteristics

Characteristic	Number (%)
Median age (range)	49 (24–71) years
Male	16 (76)
Histology	
Glioblastoma multiforme	15 (71)
Anaplastic astrocytoma	6 (29)
KPS (%)	
100	15 (71)
90	5 (24)
80	0
70	1 (5)
Therapy after ^{131}I-81C6	
X-ray therapy	20 (95)
Chemotherapy	20 (95)

Abbreviation: ^{131}I-81C6, ^{131}I-labeled murine antitenascin monoclonal antibody 81C6.

Table 2. Human antimouse 81C6 antibody response

Assay Number	Patient Number	Days after ^{131}I-81C6	Titer
1	1	13	1:128
2	1	32	1:128
3	1	123	1:128
4	2	14	1:128
5	2	28	1:128
6	3	27	1:128
7	3	83	1:128
8	3	173	1:128
9	4	28	1:256
10	6	44	1:128
11	6	110	1:128
12	7	13	1:128
13	7	41	1:256
14	8	33	1:128
15	8	96	1:128
16	9	28	1:128
17	9	98	1:128
18	10	7	1:128
19	10	34	1:128
20	11	5	1:128
21	11	39	1:128
22	11	103	1:128
23	12	13	1:128
24	13	25	1:128
25	14	13	1:128
26	15	28	1:256
27	16	25	1:128
28	17	15	1:128
29	19	96	1:128

Abbreviation: ^{131}I-81C6, ^{131}I-labeled murine antitenascin monoclonal antibody 81C6.

HAMA

Twenty-nine HAMA immunoassays were performed on 17 patients within 5–173 days of treatment. All samples were positive (Table 2), but no HAMA-related toxicity was observed.

Dosimetry Results

Table 3 provides an overview of residence times and calculated dosimetry for each patient. Of note, 20 patients (95%) achieved a 44-Gy (±10%) boost to the SCRC 2-cm margin. The one patient who did not achieve the targeted 44-Gy boost was deliberately underdosed due to difficulty aspirating cerebrospinal fluid from the SCRC immediately prior to ^{131}I-81C6 administration.

Toxicity

Minimal toxicity was attributable to ^{131}I-81C6. Three patients (14%) developed reversible grade 3 hematologic toxicity that resolved spontaneously without intervention. Two patients (10%) developed grade 3 headache within 2–4 weeks of ^{131}I-81C6 that responded to corticosteroids. Twelve patients (57%) had seizures following ^{131}I-81C6, but only four patients (19%) experienced seizures within 1 month of ^{131}I-81C6, and all but one of these patients had experienced seizures prior to ^{131}I-81C6 administration. No other grade 3 or greater, acute or delayed neurologic complications were observed. Three patients (14%) developed CNS wound infections that responded to Rickham catheter removal and intravenous antibiotics. Table 4 summarizes the frequency and type of grade 3 or greater toxicities, including additional grade 3 toxicities felt to be unrelated to ^{131}I-81C6 therapy. There were no grade 4 toxicities. One patient (5%) developed grade 2 hypothyroidism. There were two study deaths: one patient who developed septic shock following rupture of an intestinal diverticulum, and one patient due to status epilepticus.

Fourteen patients (67%) completed FACT-BR QoL and neurocognitive testing prior to ^{131}I-81C6 administration (range, 0–30 days), but only seven patients (33%) completed post-^{131}I-81C6 assessments (range, 28–174 days). Although the small sample size did not permit sufficient statistical power to conduct an adequate assessment of the effect of ^{131}I-81C6 on QoL and neurocognitive function, there were no gross differences between pre- and post-^{131}I-81C6 evaluations.

Biopsies and Reoperation

Eleven (52%) patients underwent 12 surgical procedures following ^{131}I-81C6: eight stereotactic biopsies and four craniotomies. Four biopsies (50%) showed recurrent tumor, whereas four (50%) revealed gliosis. Three craniotomies (75%) revealed recurrent tumor. One patient exhibiting gliosis on an initial stereotactic biopsy had evidence of recurrent tumor on a subsequent craniotomy. One patient with AA, who received the largest admin-

Table 3. Individual patient characteristics and dosimetry results

							SCRC		Whole Body	
Patient No.	Age	Histology	Gender	KPS	Administered Activity (mCi)	Delivered Activity to 2-cm SCRC Rim (Gy)	Volume (cm^3)	Residence Time (h)	Activity (cGy)	Residence Time (h)
1	71	GBM	M	100	25	45.1	2.3	210.0	18	37.0
2	57	GBM	F	90	42	44.8	20.0	278.4	36	37.
3	42	GBM	M	100	57	44.2	6.6	129.0	33	37.0
4	54	GBM	M	90	47	44.8	15.0	220.0	35	37.0
5	24	AA	M	90	25	46.0	4.0	250.0	20	37.0
6	59	AA	M	80	54	44.8	28.0	250.0	30	10.0
7	60	GBM	F	90	92	43.4	7.0	80.0	30	20.0
8	55	GBM	M	90	52	47.6	14.2	206.0	25	10.0
9	40	GBM	F	100	34	44.3	7.8	230.0	18	10.0
10	50	GBM	M	100	39	46.2	3.4	150.0	25	40.0
11	44	GBM	M	100	75	45.4	11.0	122.0	85	100.0
12	51	GBM	M	100	55	33.8	11.7	127.0	23	20.0
13	49	AA	M	100	90	44.6	16.7	120.0	45	30.0
14	30	AA	F	100	70	44.5	29.8	197.0	45	30.0
15	34	GBM	M	100	50	43.4	15.0	200.0	41	50.0
16	52	GBM	F	100	57	44.0	22.0	210.0	48	50.0
17	55	GBM	M	100	79	44.0	38.1	194.0	50	30.0
18	24	GBM	M	100	150	44.7	40.0	106.0	84	40.0
19	37	AA	M	100	61	44.4	11.6	150.0	67	90.0
20	42	AA	M	100	41	44.0	12.1	225.0	NA	NA
21	43	GBM	M	100	55	44.6	13.8	180.0	33	30

Abbreviations: SCRC, surgically created resection cavity; KPS, Karnofsky performance score; GBM, glioblastoma multiforme; M, male; F, female; AA, anaplastic astrocytoma; NA, not available.

istered dose of ^{131}I-81C6 among enrolled patients (150 mCi), underwent a craniotomy due to progressive MRI enhancement and edema as well as persistent grade 1–2 headaches requiring chronic corticosteroid administration. Pathology from the craniotomy revealed gliosis with no evidence of active tumor. Postoperatively, the headaches resolved and corticosteroids were successfully discontinued. This patient remained alive with an excellent QoL, including the ability to work full time, 37 months after ^{131}I-81C6 administration.

Response/Survival Data

With a median follow-up of 124.4 weeks, the median overall survival for AA patients has not been reached. With a median follow-up of 150.9 weeks, the median overall survival for GBM patients is 90.6 weeks (95% confidence interval [95% CI], 73.3–97.1 weeks; Fig. 1). One-year survival probabilities for all patients, those with GBM, and those with AA were 86% (95% CI, 72%–100%), 87% (95% CI, 71%–100%), and 83% (95% CI, 58%–100%), respectively.

Progressive disease occurred at the primary tumor site in all cases except for one patient with noncontiguous new enhancement in the ipsilateral hemisphere. In addition, one patient developed multiple new areas of

Table 4. Frequency and type of grade 3 or greater toxicity

Type	Grade 3 (%)	Grade 4 (%)	All (%)
Hematologic (all types)	3 (14)	0	3 (14)
Neutropenia	2 (10)	0	2 (10)
Thrombocytopenia	1 (4)	0	1 (4)
Anemia	0	0	0
Neurologic			
Reversible	2[a] (10)	0	2 (10)
Irreversible	0	0	0
Thrombosis	4 (20)	0	4 (20)
Wound infection	3 (14)	0	3 (14)
Transaminase elevation	2 (10)	0	2 (10)
Infection	2 (10)	0	2 (10)
Hyperglycemia	1 (4)	0	1 (4)
Avascular necrosis	1 (4)	0	1 (4)
Hyponatremia	1 (4)	0	1 (4)
Rash	1 (4)	0	1 (4)

[a]Both of these patients had grade 3 headache that resolved with corticosteroids.

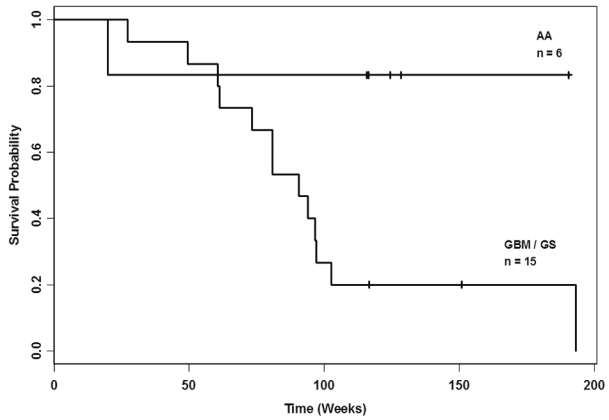

Fig. 1. Kaplan-Meier overall survival estimates for all patients following stratification by histology.

enhancement in the ipsilateral hemisphere and progressive enhancement at the primary tumor site.

Discussion

We previously demonstrated that administration of ^{131}I-81C6 into the SCRC is associated with acceptable toxicity and encouraging survival compared to historical controls for either newly diagnosed or recurrent primary malignant brain tumor patients.[4–8] However, our previous clinical trials administered a "fixed" radioactivity dose of ^{131}I-81C6 into the SCRC. Specifically, patients enrolled on our prior phase I studies received the same millicurie dose of ^{131}I-81C6 at their assigned dose level, while phase II patients were treated with the ^{131}I-81C6 MTD determined from phase I studies.

Not surprisingly, "fixed" dosing of ^{131}I-81C6 resulted in a wide range of radiation absorbed dose delivered to the SCRC margin. For example, administration of 100 mCi of ^{131}I-81C6 to recurrent patients on our phase II study delivered 18–186 Gy to the 2-cm SCRC margin.[4] Similarly, administration of 120 mCi of ^{131}I-81C6 to newly diagnosed patients delivered 24–116 Gy.[5] We therefore reasoned that a therapeutic strategy designed to deliver a consistent and optimized radiation dose to the SCRC rim for all patients may lead to greater efficacy and less toxicity.

To further evaluate this hypothesis, we retrospectively compared activity delivered to the SCRC margin, obtained from post-^{131}I-81C6 dosimetry assessments, with histopathology samples obtained from surgical procedures performed following ^{131}I-81C6 administration among patients enrolled on prior phase I and II studies. Tissue samples were available from 10 patients who achieved less than a 40-Gy boost to the SCRC rim. Nine of these tissue samples revealed recurrent tumor, and only one case demonstrated gliosis without tumor. In contrast, tissue samples from patients who achieved a greater than 48 Gy boost to the SCRC rim revealed gliosis without evidence of tumor. Patients who achieved a 44% ± 10% Gy boost appeared to have an optimal outcome with less risk of tumor recurrence and symptomatic radionecrosis.

Variables affecting radiation absorbed dose for radioimmunotherapeutics administered into a defined space include the residence time and volume of the defined space, in addition to administered activity. In our study, we calculated the SCRC volume from a pretreatment MRI and determined the SCRC residence time by administering a small dose of ^{123}I-81C6 and serially imaging the SCRC. These measurements were then used to calculate the dose of ^{131}I-81C6 predicted to achieve a 44-Gy boost to the SCRC 2-cm margin. With this approach, we successfully achieved the targeted 44-Gy boost to the SCRC in 20 of 21 (95%) treated patients. The only patient who did not achieve a 44-Gy boost deliberately received a lower dose of ^{131}I-81C6 due to inability to fully aspirate SCRC fluid prior to ^{131}I-81C6 administration. Thus, our study confirms that patient-specific ^{131}I-81C6 dosing to deliver a 44-Gy boost to the SCRC is achievable.

Patient-specific dosing of ^{131}I-81C6 appears to be associated with less neurotoxicity compared to fixed radioactivity ^{131}I-81C6 dosing. Among recurrent patients treated with 100 mCi ^{131}I-81C6 in our prior phase II study, 3 of 41 patients (7%) developed grade 3 neurotoxicity, including one patient with irreversible neuromotor deficits. Similarly, among newly diagnosed patients treated with a fixed 120-mCi dose of ^{131}I-81C6, 8 (24%) developed grade 3 neurotoxicity, including 5 (15%) with irreversible deficits. In contrast, no irreversible grade 3 or greater episodes of neurotoxicity were observed in the present study with patient-specific ^{131}I-81C6 dosing. In addition, patient-specific ^{131}I-81C6 dosing appears to be associated with a low rate of reoperation for radiation necrosis: only one patient (5%) underwent this procedure. This rate compares favorably to that reported with other strategies to boost radiation activity to the primary tumor site, such as stereotactic radiosurgery and the implantation of radioactive beads into the SCRC.[25–35] Finally, although a low rate of participation with QoL and neurocognitive testing in the present pilot study precludes a meaningful interpretation of these data, the results of such assessments will be of paramount importance in future planned clinical trials.

Patient-specific dosing of ^{131}I-81C6 is associated with encouraging antitumor activity. Our results compare favorably to those observed among newly diagnosed patients who underwent GTR with carmustine wafer (Gliadel; MGI Pharma, Inc., Minneapolis, MN, USA) placement followed by XRT (55.6 weeks),[36] and the outcome achieved with XRT plus temozolomide (64 weeks).[1] However, comparisons between these two studies and the present one are limited by the higher rate of complete resection observed among patients treated in this study relative to the other two studies.

Additionally, the outcome achieved with patient-specific ^{131}I-81C6 dosing compares favorably to that achieved using fixed-millicurie ^{131}I-81C6 dosing. Specifically, the median overall survival observed in the present study was 23% longer than that achieved with

fixed-millicurie ^{131}I-81C6 treatment among a comparable patient population.[5] Nonetheless, the encouraging results of the present study, as well as those from our previous "fixed" dose ^{131}I-81C6 studies, must be interpreted cautiously, particularly in comparison to large, randomized studies, because our ^{131}I-81C6 studies reflect a single institution experience performed, in general, in patients with good prognostic factors, including relatively young age, good performance status, and optimal resection.

We have confirmed in the present study that patient-specific ^{131}I-81C6 dosing to achieve a 44-Gy boost to the SCRC margin can be readily and consistently performed. Furthermore, this approach is associated with minimal toxicity and encouraging survival. Currently, a formal phase II study is under way to further assess the efficacy of this approach. All patients treated on this study receive ^{131}I-81C6 administered to achieve a 44-Gy dose to the SCRC followed by conventional XRT plus daily temozolomide (75 mg/m^2), followed by six adjuvant cycles of temozolomide. Furthermore, to determine whether selection of patients with good prognosis is responsible for our survival results, the FDA has approved a randomized trial in which one arm will undergo GTR, XRT, and concomitant temozolomide followed by six monthly cycles of temozolomide, and the other arm will undergo the same treatment plus a calculated dose of ^{131}I-81C6 to yield a 44-Gy radiation dose to the 2-cm tumor resection margin.

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